

Table 1. Worldwide Distribution of MTHFR C677T Allele.

Country/Ethnicity	Subjects No	Genotype			C677T Allele		C677T/C677T Genotype			Year	Ref
		+/ +/-	-/ -/-	Freq	95% CI	Freq	95% CI				
Europe											
Britain/Wales											
British	199	24	94	81	0.36	0.31 - 0.41	0.12	0.08 - 0.17	1996	91	
Leicester	222	29	97	96	0.35	0.30 - 0.39	0.13	0.09 - 0.17	1996	16	
London	161	22	63	76	0.33	0.28 - 0.39	0.14	0.08 - 0.19	1997	18	
Manchester	164	18	75	71	0.34	0.29 - 0.39	0.11	0.06 - 0.16	1997	19	
Cardiff	300	45	136	119	0.38	0.34 - 0.42	0.15	0.11 - 0.19	1998	17	
Pooled	1,046	138	465	443	0.35	0.33 - 0.37	0.13	0.11 - 0.15			
Netherlands											
* Hague	207	10	86	111	0.26	0.21 - 0.30	0.05	0.02 - 0.08	1995	82	
* Hague	111	6	42	63	0.24	0.18 - 0.30	0.05	0.01 - 0.10	1996	21	
Hague	403	38	186	179	0.33	0.29 - 0.36	0.09	0.07 - 0.12	1998	12	
* Hague+ unspecified	1,273	107	537	629	0.29	0.28 - 0.31	0.08	0.07 - 0.10	1997	96	
Rotterdam	100	7	48	45	0.31	0.24 - 0.38	0.07	0.02 - 0.12	1997	22	
Pooled	503	45	234	224	0.32	0.29 - 0.35	0.09	0.06 - 0.11			
France											
France	133	13	70	50	0.36	0.30 - 0.42	0.10	0.05 - 0.15	1997	93	
* French Caucasians	456	73	195	188	0.37	0.34 - 0.41	0.16	0.13 - 0.19	1997	23	
Pooled	133	13	70	50	0.36	0.30 - 0.42	0.10	0.05 - 0.15			
Germany											
Germany	153	11	40	49	0.20	0.16 - 0.25	0.07	0.03 - 0.11	1998	87	
Jena	104	9	46	49	0.31	0.24 - 0.37	0.09	0.03 - 0.14	1998	24	
Pooled	257	20	86	151	0.25	0.21 - 0.28	0.08	0.05 - 0.11			
Ireland and Northern Ireland											
Belfast	625	72	273	280	0.33	0.31 - 0.36	0.12	0.09 - 0.14	1996	25	
Dublin, Belfast	105	7	45	53	0.28	0.22 - 0.34	0.07	0.02 - 0.11	1996	26	
Dublin	318	41	129	148	0.33	0.29 - 0.37	0.13	0.09 - 0.17	1997	27	
* Dublin	242	20	108	114	0.31	0.26 - 0.35	0.08	0.05 - 0.12	1997	27	
Dublin	261	21	121	119	0.31	0.27 - 0.35	0.08	0.05 - 0.11	1998	89	
Pooled	1,309	141	568	600	0.32	0.31 - 0.34	0.11	0.09 - 0.12			
Italy											
South	258	39	129	90	0.40	0.36 - 0.44	0.15	0.11 - 0.19	1996	28	
* North	154	35	74	45	0.47	0.41 - 0.52	0.23	0.16 - 0.29	1997	31	
North (Veneto)	130	17	71	42	0.40	0.34 - 0.47	0.13	0.07 - 0.19	1997	36	
North (Piemonte, Liguria)	182	27	96	59	0.41	0.36 - 0.46	0.15	0.10 - 0.20	1998	92	
Center (Marche)	95	17	60	18	0.49	0.42 - 0.57	0.18	0.10 - 0.26	1998	92	

	Center (Toscana)	106	32	48	26	0.53	0.46 - 0.60	0.30	0.21 - 0.39	1998	29
*	North (Veneto)	137	25	70	42	0.44	0.38 - 0.50	0.18	0.12 - 0.25	1998	32
	South	150	28	77	45	0.44	0.39 - 0.50	0.19	0.12 - 0.25	1998	33
	South	431	78	223	130	0.44	0.41 - 0.47	0.18	0.14 - 0.22	1998	34
	Center (Lazio)	155	25	85	45	0.44	0.38 - 0.49	0.16	0.10 - 0.22	1998	35
	North (Lombardia)	353	74	166	113	0.44	0.41 - 0.48	0.21	0.17 - 0.25	1997	30
	South	193	33	102	58	0.44	0.38 - 0.49	0.17	0.12 - 0.22	1998	15
	Pooled	2,053	370	1057	626	0.44	0.42 - 0.45	0.18	0.16 - 0.20		
	Norway, Sweden										
	Norway	68	4	22	42	0.22	0.15 - 0.29	0.06	0.00 - 0.11	1997	88
	Sweden	126	13	50	63	0.30	0.24 - 0.36	0.10	0.05 - 0.16	1998	37
	Pooled	194	17	72	105	0.27	0.23 - 0.32	0.09	0.05 - 0.13		
	Africa and Middle East										
	Sub-Saharan Africa										
	sub-Saharan African	234	0	31	203	0.07	0.04 - 0.09	0.00	0.00 - 0.00	1998	51
*	sub-Saharan African	89	NA	NA	NA	0.07	0.03 - 0.11	NA	NA - NA	1998	52
	Zaire, Cameroon	67	0	7	60	0.05	0.01 - 0.09	0.00	0.00 - 0.00	1998	54
	Pooled	301	0	38	263	0.06	0.04 - 0.08	0.00	0.00 - 0.00		
	Middle East										
	Yemen	46	1	14	31	0.17	0.09 - 0.26	0.02	0.00 - 0.06	1998	51
	Turkey	93	7	39	47	0.28	0.22 - 0.35	0.08	0.02 - 0.13	1998	90
	Asia										
	Asians	346	12	98	236	0.18	0.15 - 0.21	0.03	0.02 - 0.05	1998	51
	Japan	129	14	70	45	0.38	0.32 - 0.44	0.11	0.05 - 0.16	1996	66
	Japan	419	51	214	154	0.38	0.34 - 0.41	0.12	0.09 - 0.15	1997	60
	Japan	778	79	361	338	0.33	0.31 - 0.36	0.10	0.08 - 0.12	1997	64
*	Japan	98	11	49	38	0.36	0.29 - 0.43	0.11	0.05 - 0.17	1997	62
	Japan	260	29	135	96	0.37	0.33 - 0.41	0.11	0.07 - 0.15	1997	62
	Japan	325	33	139	153	0.32	0.28 - 0.35	0.10	0.07 - 0.13	1997	64
	Japan	105	19	51	35	0.42	0.35 - 0.49	0.18	0.11 - 0.25	1998	65
	Japan	310	42	158	110	0.39	0.35 - 0.43	0.14	0.10 - 0.17	1998	67
	Japan	146	17	43	86	0.26	0.21 - 0.32	0.12	0.06 - 0.17	1998	61
	Pooled Japan	2,472	284	1171	1017	0.35	0.34 - 0.37	0.11	0.10 - 0.13		
	South Pacific										
	Australia, Sydney	225	24	113	88	0.36	0.31	0.40	0.11	0.07	0.15
										1996	38
	Americas										
	Latin America										
	Brazil, whites	107	11	58	38	0.37	0.31 - 0.44	0.10	0.05 - 0.16	1998	53

Colombians	150	38	70	42	0.49	0.43 - 0.54	0.25	0.18 - 0.32	1998	68
Brazil, blacks	137	2	51	84	0.20	0.15 - 0.25	0.01	0.00 - 0.03	1998	53
Brazil, blacks	50	1	10	39	0.12	0.05 - 0.19	0.02	0.00 - 0.06	1998	54
Amerindians (Brazil)	129	10	42	77	0.24	0.19 - 0.29	0.08	0.03 - 0.12	1998	54
Amerindians (Brazil)	39	8	19	12	0.45	0.33 - 0.57	0.21	0.08 - 0.33	1998	51
Amerindians (Brazil)	83	1	17	65	0.11	0.06 - 0.17	0.01	0.00 - 0.04	1998	53
Amerindians (Cayapa, Ecuador)	57	NA	NA	NA	0.43	0.34 - 0.52	NA	NA	1998	52
Pooled Blacks (Brazil)	187	3	61	123	0.18	0.14 - 0.22	0.02	0.00 - 0.03		
Canada										
Quebec	293	46	122	125	0.37	0.33 - 0.40	0.16	0.12 - 0.20	1996	40
Quebec	121	13	61	47	0.36	0.30 - 0.42	0.11	0.05 - 0.16	1997	39
Pooled (Quebec)	414	59	183	172	0.36	0.33 - 0.40	0.14	0.11 - 0.18		
United States										
Whites, California	269	32	122	115	0.35	0.30 - 0.39	0.12	0.08 - 0.16	1998	50
Whites, South Carolina	151	20	65	66	0.35	0.29 - 0.40	0.13	0.08 - 0.19	1997	58
Whites, Oregon	133	20	63	50	0.39	0.33 - 0.45	0.15	0.09 - 0.21	1996	40
Whites, Washington	338	43	141	154	0.34	0.30 - 0.37	0.13	0.09 - 0.16	1997	49
Whites, unspecified	101	9	43	49	0.30	0.24 - 0.37	0.09	0.03 - 0.14	1996	57
Whites, unspecified	155	12	78	65	0.33	0.28 - 0.38	0.08	0.04 - 0.12	1997	42
Pooled, whites	1,147	136	512	499	0.34	0.32 - 0.36	0.12	0.10 - 0.14		
Blacks, California	17	2	4	11	0.24	0.08 - 0.39	0.12	0.00 - 0.27	1998	50
Blacks, Georgia	185	4	29	152	0.10	0.07 - 0.13	0.02	0.00 - 0.04	1998	55
Blacks, North-East	46	0	9	37	0.10	0.03 - 0.16	0.00	0.00 - 0.00	1998	56
Blacks, South Carolina	146	0	65	81	0.22	0.17 - 0.27	0.00	0.00 - 0.00	1997	58
Blacks, unspecified	102	0	20	82	0.10	0.05 - 0.14	0.00	0.00 - 0.00	1996	57
Pooled, blacks	496	6	127	363	0.14	0.12 - 0.16	0.01	0.00 - 0.02		
Hispanics, California	169	35	71	63	0.42	0.36 - 0.47	0.21	0.15 - 0.27	1998	50
Other races, California	48	3	16	29	0.23	0.14 - 0.32	0.06	0.00 - 0.13	1998	50
Boston	188	27	90	71	0.38	0.33 - 0.43	0.14	0.09 - 0.19	1996	48
South Carolina, unspecified	109	5	36	68	0.21	0.15 - 0.27	0.05	0.01 - 0.09	1996	85
Physicians	290	39	116	135	0.33	0.30 - 0.37	0.13	0.10 - 0.17	1997	45
Cancer-free subjects	326	49	132	145	0.35	0.32 - 0.39	0.15	0.11 - 0.19	1997	46
USA, unspecified	627	84	263	280	0.34	0.32 - 0.37	0.13	0.11 - 0.16	1996	43
USA, unspecified	170	28	77	65	0.39	0.34 - 0.44	0.17	0.11 - 0.22	1996	40
USA, unspecified	365	45	170	150	0.36	0.32 - 0.39	0.12	0.09 - 0.16	1996	44
USA, unspecified	554	59	238	257	0.32	0.29 - 0.35	0.11	0.08 - 0.13	1997	41
USA, unspecified	500	72	200	228	0.34	0.31 - 0.37	0.14	0.11 - 0.17	1998	47
Pooled unspecified	3,129	408.1	1322	1399	0.34	0.33 - 0.35	0.13	0.12 - 0.14		
Pooled USA	3,503	322	1365	1816	0.29	0.28 - 0.30	0.09	0.08 - 0.10		

* Not included in pooled estimate for lack of data or overlap with other studies

Table 2. Association between MTHFR genotypes and risk of neural tube defects, by gene variant and family member (1995-1999)

Country	Cases No.	Case genotype (*)			Controls No.			Control genotype (*)			Odds Ratio (95%CI) +/- vs. -/-	Odds Ratio (95%CI) +/- vs. -/-	AF% (H) +/-	Source (#)	Year	Ref.
		+/-	+/-	-/-	+/-	+/-	-/-	+/-	+/-	-/-						
I. C677T variant																
Infant																
§ Netherlands	55	7	26	22	207	10	86	111	3.53 (1.07-11.6)	1.52 (0.77-3.01)	9.1	16.2	3	1995	82	
Netherlands	86	10	42	34	403	36	162	205	1.67 (0.70-3.91)	1.56 (0.95-2.57)	4.7	17.5	3	1998	12	
Ireland	82	15	32	35	99	6	43	50	3.57 (1.15-11.6)	1.06 (0.54-2.09)	13.2	2.2	3	1995	83	
§ Ireland	153	29	-	-	242	20	108	114	2.61 (1.41-4.78)	-	-	-	3	1996	84	
§ Ireland	130	26	-	-	442	39	-	-	2.60 (1.50-4.40)	-	-	-	3	1997	86	
Ireland	271	51	119	101	242	20	108	114	2.88 (1.55-5.38)	1.24 (0.84-1.84)	12.3	8.5	3	1999	94	
UK	41	5	20	16	199	24	94	81	1.05 (0.30-3.51)	1.08 (0.49-2.35)	0.6	3.6	4	1996	91	
France	43	3	21	19	133	13	70	50	0.61 (0.12-2.67)	0.79 (0.36-1.72)	-	-	4	1997	93	
Norway	28	1	15	12	68	4	22	42	0.88 (0.03-9.96)	2.39 (0.87-6.63)	-	31.2	4	1997	88	
Germany	137	14	44	79	153	11	40	49	0.79 (0.31-2.04)	0.68 (0.38-1.24)	-	-	4	1998	87	
Turkey	49	4	25	20	93	7	39	47	1.34 (0.29-5.96)	1.51 (0.69-3.32)	2.1	17.2	4	1998	90	
USA	41	9	15	17	109	5	36	68	7.20 (1.87-29.0)	1.67 (0.69-4.01)	18.9	14.7	3	1996	85	
USA	214	41	100	73	503	72	213	218	1.70 (1.04-2.78)	1.40 (0.97-2.03)	7.9	13.4	1	1998	50	
Italy	203	52	89	62	583	97	313	173	1.50 (0.94-2.39)	0.79 (0.54-1.17)	8.5	-	3	1998	92	
Pooled	1195	205	522	468	2585	295	1140	1097	1.73 (1.39-2.16)	1.15 (0.98-1.34)	6.1	5.0				
Mother																
§ Netherlands	70	11	27	32	207	10	86	111	3.82 (1.35-10.8)	1.09 (0.58-2.03)	11.6	3.2	3	1995	82	
Netherlands	100	18	38	44	403	36	162	205	2.33 (1.15-4.69)	1.09 (0.66-1.82)	10.3	3.1	3	1998	12	
UK	36	5	15	16	199	24	94	81	1.05 (0.30-3.51)	0.81 (0.35-1.85)	0.7	-	4	1996	91	
USA	65	9	31	25	65	6	29	30	1.80 (0.49-6.71)	1.28 (0.58-2.86)	6.2	10.4	4	1997	97	
Ireland	82	13	35	34	260	21	121	118	2.15 (0.91-5.07)	1.00 (0.57-1.78)	8.5	0.0	2	1998	89	
Ireland	218	30	108	80	242	20	108	114	2.14 (1.08-4.23)	1.43 (0.95-2.15)	7.3	14.9	3	1999	94	
Turkey	40	7	16	17	93	7	39	47	2.76 (0.73-10.6)	1.13 (0.47-2.73)	11.2	4.6	4	1998	90	
Pooled	541	82	243	216	1262	114	553	595	2.05 (1.47-2.86)	1.17 (0.93-1.46)	8.1	2.0				
Father																
§ Netherlands	60	6	25	29	207	10	86	111	2.30 (0.67-7.64)	1.11 (0.58-2.13)	5.7	4.1	3	1995	82	
Netherlands	86	8	40	38	403	36	162	205	1.20 (0.47-2.96)	1.33 (0.79-2.24)	1.6	11.5	3	1998	12	
UK	26	4	14	8	199	24	94	81	1.69 (0.39-6.97)	1.51 (0.56-4.17)	6.3	18.2	4	1996	91	
USA	55	4	27	24	55	5	24	26	0.87 (0.17-4.36)	1.22 (0.52-2.87)	-	8.9	4	1997	97	
Turkey	33	2	17	14	93	7	39	47	0.96 (0.12-6.04)	1.46 (0.59-3.62)	-	16.2	4	1998	90	
Pooled	260	24	123	113	957	82	405	470	1.18 (0.65-2.12)	1.36 (0.96-1.91)	1.4	12.3				
II. A1298C variant																
Infant																
Netherlands	86	8	41	37	403	38	186	179	1.02 (0.40-2.51)	1.07 (0.64-1.79)	0.3	6.5	3	1998	12	
Mother																
Netherlands	100	6	43	51	403	38	186	179	0.55 (0.20-1.47)	0.81 (0.50-1.31)	-	-	3	1998	12	
Father																
Netherlands	86	10	39	37	403	38	186	179	1.27 (0.54-2.95)	1.01 (0.60-1.71)	4.5	1.0	3	1998	12	

(*) 1, population-based registry; 2, Hospital-based cohort; 3, Patient/parent groups; 4, Convenient sample or undefined.

(†) +, variant allele. -, normal or common allele

(‡) AF, Attributable Fraction

(§) Excluded from pooled estimate because of lack of data or overlap with other studies

Appendix Table. Notes on populations listed in Table 1, worldwide Distribution of MTHFR C677T Allele.

Country/Ethnicity	Subjects (No.)	Year	Ref	First Author	Notes on choice of population
Europe					
Britain/Wales					
British	199	1996	91	Papapetrou et al	Volunteers of British origin, not otherwise specified (nos)
Leicester	222	1996	16	Adams et al	Adult visitors to hospital patients without cardiovascular illnesses
London	161	1997	18	Markus et al	White spouses of white patients with ischemic disease
Manchester	164	1997	19	Salden et al	Healthy plasma donors, nos
Cardiff	300	1998	17	Bowen et al	Blood samples from Blood Transfusion unit and Haematology Lab
Pooled	1046				
Netherlands					
* Hague	207	1995	82	van der Put et al	Hague volunteers
* Hague	111	1996	21	Kluijtmans et al	Hague volunteers
Hague	403	1998	12	van der Put et al	Hague volunteers
* Hague+ unspecified	1273	1997	96	van der Put et al	Four published studies pooled with 833 unpublished controls (selection unspecified)
Rotterdam	100	1997	22	Verhoeft et al	Random sample of 100,000 pop based sample (response rate, 62%)
Pooled	503				
France					
France	133	1997	93	Mornet et al	103 from DNA bank, 30 volunteers NOS
* French Caucasians	456	1997	23	Brulhart et al	Patients with non-insulin dependent diabetes
Pooled	133				
Germany					
Germany	153	1998	87	Koch et al	Healthy individuals 'randomly selected from the population' (nos)
Jena	104	1998	24	Reinhardt et al	Healthy volunteers, nos
Pooled	257				
Ireland and Northern Ireland					
Belfast	625	1996	25	Harmon et al	
Dublin, Belfast	105	1996	26	Gallagher et al	61 employees (Dublin) + 44 patients at random from GP practices (Belfast); 75% male
Dublin	318	1997	27	Molloy et al	Female hospital staff & students
* Dublin	242	1997	27	Molloy et al	Pregnant women, sampled from cohort of over 50,000 such women
Dublin	261	1998	89	Molloy et al	Pregnant women, sampled from cohort of over 50,000 such women
Pooled	1309				
Italy					
South	258	1996	28	de Franchis et al	Healthy persons without vascular disease, nos
* North	154	1997	31	Cattaneo et al	Population may overlap with Sacchi et al (see below)
North (Veneto)	130	1997	36	Tosetto et al	Population based (65% response rate)
North (Piemonte, Liguri	182	1998	92	de Franchis et al	Newborns, metabolic screening program (healthy volunteers excluded)
Center (Marche)	95	1998	92	de Franchis et al	Newborns, metabolic screening program (healthy volunteers excluded)
Center (Toscana)	106	1998	29	Abbate et al	Healthy subjects, nos
* North (Veneto)	137	1998	32	Girelli et al	Patients referred to cardiac surgery center, but without abnormal coronaries
South	150	1998	33	Grandone et al	Healthy women of parity one or more
South	431	1998	34	Margaglione et al	Healthy individuals, NOS (57% males)
Center (Lazio)	155	1998	35	Motti et al	Healthy university employees
North (Lombardia)	353	1997	30	Sacchi E et al	Healthy individuals , nos
South	193	1998	15	Ames	Healthy subjects, nos
Pooled	2053				
Norway, Sweden					
Norway	68	1997	88	Bjørke-Monsen et al	
Sweden	126	1998	37	Kostulas et al	
Pooled	194				
Africa and Middle East					
Sub-Saharan Africa					
sub-Saharan African	234	1998	51	Schneider et al	

*	sub-Saharan African	89	1998	52 Pepe et al	
	Zaire, Cameroon	67	1998	54 Franco et al	
	Pooled	301			
Middle East					
	Yemen	46	1998	51 Schneider et al	
	Turkey	93	1998	90 Boduroglu et al	
Asia					
	Asians	346	1998	51 Schneider et al	
	Japan	129	1996	66 Nishio et al	Random selection from a cohort of male graduates from a medical school
	Japan	419	1997	60 Arinami et al	
*	Japan	778	1997	64 Morita et al	
	Japan	98	1997	62 Satoshi	Pregnant women
	Japan	260	1997	62 Satoshi	Only the healthy nonpregnant controls included here
	Japan	325	1997	64 Morita et al	
	Japan	105	1998	65 Nakata et al	
	Japan	310	1998	67 Ou et al	
	Japan	146	1998	61 Neugebauer et al	Healthy volunteers, nos
	Pooled Japan	2472			
South Pacific					
	Australia, Sydney	225	1996	38 Wilcken et al	
Americas					
Latin America					
	Brazil, whites	107	1998	53 Arruda et al	Students and staff of Sao Paulo University
	Colombians	150	1998	68 Vanegas Olga Camacho et al	
	Brazil, blacks	137	1998	53 Arruda et al	Students and staff of Bahia University
	Brazil, blacks	50	1998	54 Franco et al	
	Amerindians (Brazil)	129	1998	54 Franco et al	5 tribes
	Amerindians (Brazil)	39	1998	51 Schneider et al	Unspecified tribe(s)
	Amerindians (Brazil)	83	1998	53 Arruda et al	Parakana tribe (Tupi)
	Amerindians (Cayapa, I)	57	1998	52 Pepe et al	Cayapa tribe
	Pooled Blacks (Brazil)	187			
Canada					
	Quebec	293	1996	40 Deloughery et al	"Randomly chosen" newborns from genetic screening program in Quebec
	Quebec	121	1997	39 Christensen et al	"White-collar workers" from utility company, healthy
	Pooled (Quebec)	414			
United States					
	Whites, California	269	1998	50 Shaw et al	
	Whites, South Carolina	151	1997	58 Stevenson et al	
	Whites, Oregon	133	1996	40 Deloughery et al	
	Whites, Washington	338	1997	49 Schwartz et al	
	Whites, unspecified	101	1996	57 McAndrew et al	
	Whites, unspecified	155	1997	42 Brugada et al	
	Pooled, whites	1147			
	Blacks, California	17	1998	50 Shaw et al	
	Blacks, Georgia	185	1998	55 Dilley et al	
	Blacks, North-East	46	1998	56 Giles et al	
	Blacks, South Carolina	146	1997	58 Stevenson et al	
	Blacks, unspecified	102	1996	57 McAndrew et al	
	Pooled, blacks	496			
	Hispanics, California	169	1998	50 Shaw et al	
	Other races, California	48	1998	50 Shaw et al	
	Boston	188	1996	48 Schmitz et al	
	South Carolina, unspec	109	1996	85 Ou et al	
	Physicians	290	1997	45 Ma et al	

Cancer-free subjects	326	1997	46 Ma et al
USA, unspecified	627	1996	43 Chen et al
USA, unspecified	170	1996	40 Deloughery et al
USA, unspecified	365	1996	44 Jacquis et al
USA, unspecified	554	1997	41 Anderson et al
USA, unspecified	500	1998	47 Verhoef et al
Pooled unspecified	3129		
Pooled USA	3503		

* Not included in pooled estimate for lack of data or overlap with other studies